Remarks

Amendments to the Claims

The claims as originally filed were originally restricted into four groups. The claims in this application were those divided into group II, claims 1-13 and 30-32, drawn to ""methods for determining the concentration or relative ratio of lipoprotein particles in a biological sample". Please note that there is an error in the office action as to which claims are currently pending.

Upon review of the claims, it was unclear that this aspect of the invention had been clearly defined. The claims have therefore been amended to recite the determination of the relative ratios of different lipoproteins such as HDL and LDL or apoproteins, such as Apo C-III and Apo E. Support is found, for example, at page 14, lines 23-34, and page 34, lines 12-27; see also example 9 at pages 65-66; example 10, at pages 66-67, and example 11, at pages 67-71. Support for the monoclonal antibodies which react with HDL or LDL is found for LDL at page 26, line 30, to page 28, line 10; for antibodies to HDL, page 28, line 11, to page 29, line 13. This section also describes other antibodies specific for the different apolipoproteins.

Rejections under 35 U.S.C. §112

The specification was objected to and claims 6 and 9 rejected under 35 U.S.C. §112. These rejections are respectfully traversed.

Enclosed is a Declaration of Availability of Deposit showing the availability of the deposited, claimed antibodies.

Claim 6 has been amended to correct the reference to apolipoprotein lipid, to use a clearer reference to the lipid which associates with apolipoprotein. Claim 9 has been amended as

suggested by the Examiner.

Rejections under 35 U.S.C. §102(b)

Claims 1, 2, 10 and 11 were rejected under 35 U.S.C. §102(b) as disclosed by Forster, et al., Biochem. Soc. Trans. 18(6):1180 (December 1990). This rejection is respectfully traversed.

The limitation of claim 3 that the antibodies are monoclonal antibodies has been incorporated into the independent claim 1. It has also been incorporated into independent claim 12 although this claim was not rejected. As discussed in more detail below, advantages are obtained using monoclonal antibodies that cannot be obtained using polyclonal antibodies.

Rejections under 35 U.S.C. §103

Claims 1, 2, 3, 10, 11, 12 and 13 were rejected under rejections under 35 U.S.C. §103 as obvious over EPA 0 257 778 by Scripps Clinic in combination with Forster, et al. Claims 1, 2, 3, and 6 were rejected under 35 U.S.C. §103 over EP 0 407 035 by Luca in combination with Forster, et al. Claims 7 and 8 were rejected under 35 U.S.C. §103 as obvious over EP 0 407 035 by Luca, in view of Forster, et al. and Mills, et al., Laboratory Techniques in biochemistry and molecular biology, vol. 14, A Guidebook to Lipoprotein Technique, pp. 472-478 (1984). Claims 1, 2, 3, 10, 11, 12 and 13 were rejected under 35 U.S.C. §103 over EP 0 257 778 by Scripps Clinic in combination with U.S. Patent 4,786,589 to Rounds. Claim 9 is rejected under 35 U.S.C. §103 over EP 0 407 035 by Luca in combination with Rounds et al. and Forster, et al. These rejections are respectfully traversed if applied to the amended claims.

Scripps

Scripps describes a standard sandwich type immunoassay for apo B-100 – i.e., an assay for apolipoprotein B which does not distinguish between types of apolipoprotein nor apolipoprotein which is specific to HDL, LDL or VLDL. The entire focus of the application is on a single monoclonal antibody which inhibits LDL binding and uptake.

Forster, et al.

Forster et al. indicates the desirability of developing a dipstick for detection of apolipoproteins. It further states that it would be desirable to provide a dipstick that would distinguish between apo A1 and apo B, but fails to state how this could be achieved, nor where such antibodies obtained.

Luca

Luca describes methods for measuring apoproteins by solid phase immunoassays. There is much discussion of measuring both LMD and EEID, defined as lipid moieties and apoprotein expressed epitope immunoreactivity, respectively.

Rounds

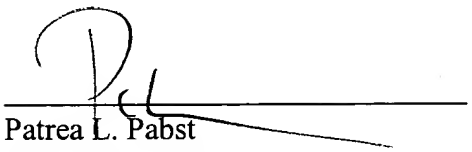
Rounds merely provides methods and reagents to make immunoassay dipsticks.

None of the cited art discloses dipsticks which can be used to determine the relative concentrations of HDL and LDL or different apolipoproteins. Therefore, none of the art enables nor makes obvious the subject matter of the amended claims.

Allowance of claims 1-13 and 30-32, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an Appendix to facilitate review by the

Examiner.

Respectfully submitted,



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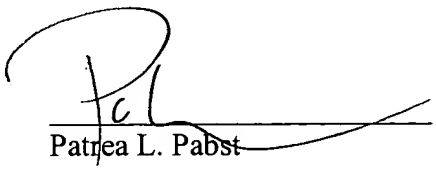

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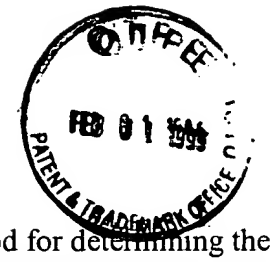

APPENDIX: Pending Claims

1. (amended) A method for determining the [concentration of a specific lipoprotein, an apolipoprotein, or lipid associated with a specific lipoprotein] relative ratio of LDL to HDL or at least two different apolipoproteins in a biological sample comprising:

immersing into the sample a solid phase material having separately immobilized thereon at least first and second monoclonal antibody molecules immunoreactive with a specific lipoprotein [or apolipoprotein] indicative of LDL or HDL or at least two different apolipoproteins;

allowing the monoclonal antibody molecules time to bind to the lipoprotein [or apolipoprotein] in the LDL and HDL or apolipoproteins in the sample;

removing the solid phase material containing the immobilized monoclonal antibody molecules; [and]

determining the amount of LDL and HDL lipoprotein [, apolipoprotein, or lipid associated with a lipoprotein] or at least two different apolipoproteins bound by the immobilized monoclonal antibody molecules,and

comparing the amount bound which is specific for LDL or HDL or each apolipoprotein in order to calculate the relative amounts of LDL and HDL or apolipoproteins.

2. The method of claim 1 wherein the antibody molecules immobilized on the solid phase material are immunoreactive with a lipoproteins selected from the group consisting of HDL, LDL, VLDL, and combinations thereof.

3. (amended) The method of claim 2 wherein the antibody is selected from the group consisting of [monoclonal antibodies,] recombinant antibodies[,] and antibody fragments.

4. The method of claim 3, wherein the antibody is the anti-LDL monoclonal antibody produced by the hybridoma cell line HB_3cB_3 ATCC designation number HB 11612.

5. The method of claim 3, wherein the antibody is a recombinant anti-LDL $RcB_3M_1D_4$ ATCC designation number 69602.

6. (amended) The method of claim 1 wherein the amount of lipoprotein[,] or [apolipoprotein] lipid associating with apolipoprotein is determined by staining of the material bound to the immobilized antibody using a lipid stain.

7. The method of claim 6 wherein the lipid stain is selected from the group consisting of Sudan Red 7B, Oil Red O, and Sudan Black B.

8. The method of claim 6 wherein the lipoprotein lipid is stained prior to immersing the immobilized antibodies.

9. (amended) The method of claim 6, further comprising a third antibody immunoreactive with apolipoprotein [which] wherein the third antibody is coupled to a protein stain and used to stain lipoprotein in the sample, prior to immersing into the sample the immobilized first antibodies which then bind to the stained second antibody-bound apolipoprotein.

10. The method of claim 1, wherein the apolipoprotein is selected from the group consisting of Apo A-I, Apo A-II, Apo B, Apo C-III, and Apo E.

11. The method of claim 1, wherein the biological sample is selected from the group consisting of blood, plasma, and serum.

12. (amended) A method of determining the relative concentration of [an apolipoprotein] at least two different apolipoproteins in a biological sample comprising:

mixing [an] a first and second monoclonal antibody molecules each immunoreactive with a specific apolipoprotein into the sample;

allowing the monoclonal antibody molecules to bind to the apolipoprotein in the sample,

immersing into the mixture [a second] third immobilized monoclonal antibody molecules immunoreactive with a second, distinct epitope of [the] an apolipoprotein,

allowing the [second] immobilized monoclonal antibody molecules to bind to the apolipoprotein,

detecting the presence of the apolipoprotein bound by both both monoclonal antibodies, and

determining the amount of each apolipoprotein bound by both monoclonal antibodies.

13. The method of claim 12 wherein the apolipoprotein is apolipoprotein Apo B-100.

30. (amended) A method for making a composition comprising

immobilizing on a solid phase material antibody molecules immunoreactive with a specific lipoprotein or apolipoprotein epitope present in either LDL or HDL, wherein the antibody molecules are selected from the group consisting of monoclonal antibodies, recombinant antibodies, and fragments thereof.

31. The method according to claim 30 wherein the antibody molecule is specifically immunoreactive with LDL.

32. The method of claim 30 wherein the apolipoprotein is selected from the group consisting of Apo A-I, Apo A-II, Apo B, Apo C-III, and Apo E.